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A Highly Stereoselective, Modular Route to (*E*)-Vinylsulfones and to (*Z*)- and (*E*)-Alkenes

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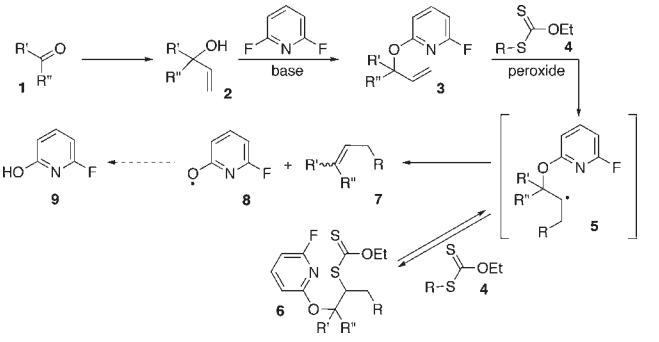
Supporting Information

ABSTRACT: A recently discovered radical fragmentation of 2-fluoro-6-pyridinoxy derivatives allows a new highly stereoselective and convergent route to (*E*)-vinylsulfones from allylic alcohols. Reductive desulfonylation or nickel-catalyzed couplings furnish di- and trisubstituted (*E*)- and (*Z*)-alkenes.

Devising flexible routes to di- and trisubstituted (*E*)- and (*Z*)-alkenes remains a major challenge in organic synthesis. Not only are these motifs ubiquitous in natural products, but they are also starting points for a vast number of ionic, radical, and carbene-based reactions and for many transition-metal-mediated transformations.[1] While several methods allow selective access to the thermodynamically more stable (*E*)-alkenes, the synthesis of the less stable isomeric (*Z*)-alkenes is often problematic. The few classical reactions, such as partial hydrogenation of triple bonds with poisoned catalysts or the salt-free variation of the Wittig reaction,[2,3] including the Stork and Zhao modification,[4] the Still−Gennari modifications of the Horner−Wadsworth−Emmons condensation,[5] in addition to the Peterson olefination[6] and various organometallic couplings,[7] occasionally exhibit limitations due to incompatibility with other functional groups or the relative inaccessibility of the precursors. Very recently, efforts have been deployed to access (*Z*)-alkenes by controlling the stereochemistry of the powerful metathesis reaction.[8]

Over a quarter of a century ago, Julia and co-workers reported the highly stereoselective reduction of vinylsulfones using sodium dithionite.[9] However, this transformation has not met with a popularity commensurate with its potential, in part because of a lack of convenient and general access to vinylsulfones with well-defined geometries. The most generally employed route to vinylsulfones is through a base-induced ionic elimination of a leaving group β to the sulfone.[10] While (*E*)- or (*Z*)-vinylsulfones may be obtained stereoselectively by treating respectively *erythro*- or *threo*-β-tosyloxy sulfones with base, this imposes prior separation of the diastereoisomeric β-tosyloxy sulfones, with the resulting serious loss in efficiency and yield.[9a] In contrast, exposure of either *erythro*- or *threo*-β-acetoxy sulfones to powdered potassium hydroxide in dry dioxane furnishes (*E*)-vinylsulfones stereoselectively;[9a] however, this latter approach is capricious, since even slight variations in the experimental conditions cause the formation of mixtures of (*E*)- and (*Z*)-vinylsulfones.[9a,b] These practical limitations in the conventional ionic routes have hampered the widespread application of the Julia reduction.[11] We have now found that by exploitation of a recently discovered *slow radical fragmentation* of fluoropyridyloxy derivatives of vinylsulfones, a convenient access to (*E*)-vinylsulfones in high stereochemical purity can be secured. This translates into a powerful method for the assembly of complex stereodefined alkenes when combined with the Julia desulfonylation. Radical reactions have had a very limited impact on the stereoselective synthesis of alkenes, especially as regards access to the more precious (*Z*)-isomers.[12]

Scheme 1. Formation of Alkenes from Allylic Alcohols



The conversion of allylic alcohols **2** into their 2-fluoropyridyloxy derivatives **3** allows β-scission of the carbon−oxygen bond by a homolytic mechanism.[13] Homolytic cleavage of the normally strong carbon−oxygen bond to give oxygen-centered radicals is relatively rare, and apart from the particular case of epoxides,[14] it occurs only in special situations of currently limited synthetic significance.[15] Indeed, the general absence of such fragmentations is a hallmark of radical processes, which have proved effective for the selective modification of oxygenated synthetic intermediates and natural products (e.g., carbohydrates). Nevertheless, homolysis of carbon−oxygen bonds under mild conditions through easily accessible derivatives opens numerous synthetic opportunities not hitherto available, in particular for the synthesis of alkenes **7** starting from various aldehydes and ketones **1** (Scheme 1).[13]

The radical addition of xanthate **4** to derivative **3**, which is easily prepared from allylic alcohol **2** by reaction with commercially available 2,6-difluoropyridine in the presence of base, produces alkene **7** and fluoropyridinoxyl radical (**8**). The latter is mostly converted into 2-fluoro-6-hydroxypyridine (**9**). The (*E*)-alkene is the major and, in some favorable cases, the sole geometrical isomer. This indicates that β-elimination of fluoropyridinoxyl radical **8** at the level of adduct radical **5** *is sufficiently slow (in relative terms) with respect to rotation around the various bonds*, allowing the molecule to adopt a propitious transition

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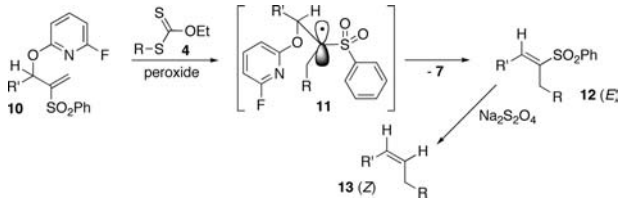
Scheme 2. Stereoselective Fragmentation Leading to (*E*)-Vinylsulfones

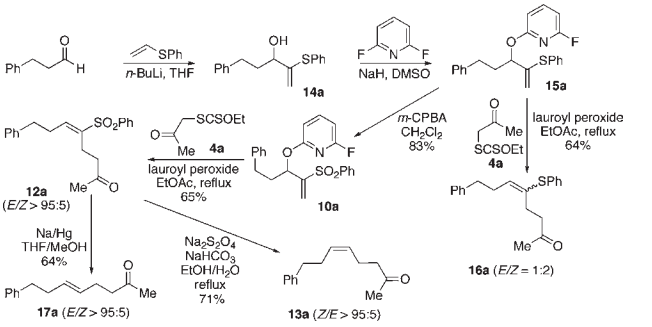


conformation with minimal steric repulsion. Indeed, in our preliminary work it even proved possible in some examples to isolate addition products **6** where no elimination had taken place, showing clearly that the *intermolecular* exchange of the xanthate group can be much faster than the *unimolecular* elimination step. While this has no consequence for the final outcome because the reversibility of the xanthate exchange means that intermediate adduct radical **5** is continuously regenerated, the relative slowness of the elimination means that control of the stereochemistry by an appropriate choice of substituents can indeed be possible. A bulky sulfone group on the starting alkene, as in **10** (Scheme 2), should exert sufficient steric pressure in transition structure **11** to force an anti disposition of the sulfone and R′ groups and thus direct the elimination toward (*E*)-vinylsulfone **12** in a highly stereoselective if not exclusive manner. Desulfonylation with overall retention, according to the Julia procedure, would then deliver the desired (*Z*)-alkene **13**.

From dihydrocinnamaldehyde as a test starting aldehyde, the corresponding vinyl sulfide **15a** was prepared by addition of the vinyl anion derived from phenyl vinyl sulfide[16] followed by treatment of the resulting allylic alcohol **14a** with 2,6-difluoropyridine in the presence of sodium hydride (Scheme 3). Not unexpectedly, the reaction of xanthate **4a** with vinyl sulfide derivative **15a** in the presence of stoichiometric lauroyl peroxide in refluxing ethyl acetate gave the corresponding radical addition−fragmentation product **16a**, but with poor stereoselectivity in favor of the *Z* isomer. Oxidation of vinyl sulfide **15a** with 2 equiv of *m*-chloroperoxybenzoic acid (*m*-CPBA) delivered sulfone analogue **10a** in good yield. Fortunately, no concomitant oxidation of the pyridine nitrogen took place. We were indeed concerned that the known formation of *N*-oxides from 2-fluoropyridines by reaction with peracid would prove to be a serious complication and an eventual setback.[17] In contrast to the case of sulfide **15a**, addition of xanthate **4a** to vinylsulfone **10a** under the same conditions resulted in the formation of addition−elimination product **12a** nearly exclusively as the *E* isomer.[18] It is noteworthy that an acetonyl radical with an *electrophilic* character could be successfully added to an *electrophilic* vinylsulfone. It is one of the prominent features of the xanthate process that the intermediate radicals are given a sufficient lifetime to allow them to undergo relatively slow reactions that would be quite difficult to accomplish with other radical-based methods.[19]

Exposure of vinylsulfone **12a** to a refluxing ethanolic solution of sodium dithionite and sodium bicarbonate resulted in a smooth desulfonylation to give the desired (*Z*)-alkene **13a** in good yield with high stereochemical purity (Scheme 3). Interestingly, desulfonylation using sodium amalgam furnished the isomeric (*E*)-alkene **17a**. These conditions are known to deliver the more stable (*E*)-alkene irrespective of the stereochemistry of the starting vinylsulfone.[8] It is thus possible to prepare at will either geometrical isomer of the alkene from the same vinylsulfone precursor.

Scheme 3. Stereoselective Synthesis of (*E*)- and (*Z*)-Alkenes



The stereoselective formation of vinylsulfones was extended to more complex derivatives, as shown by the examples compiled in Table 1 (OFPy = 2-fluoropyridin-6-oxyl). Precursors **10b**−**h** were prepared from various aldehydes and ketones by the same three-step sequence used for **10a** and outlined in Scheme 3 (see the Supporting Information). Except for **12f** and **12g**, where a 2:1 *E*:*Z* ratio was observed, the selectivity for the *E* isomer of vinylsulfones **12** was greater than 20:1; in fact, none of the *Z* isomer could be detected by NMR analysis of the crude reaction mixture in most instances. The low selectivity in the case of ketone-derived vinylsulfones **12f** and **12g** reflects the relatively small difference in the steric bulk of the substituents and the faster (and therefore less stereroselective) cleavage of the weaker tertiary C−O bond. Stereodefined tetrasubstituted vinylsulfones such as **12h** and **12i** may be produced when a really bulky *tert*-butyl substituent is present to bias the fragmentation.

The process is tolerant of numerous useful functional groups, such as Weinreb amides (**12b** and **12j**), masked α-ketoaldehydes (**12d**), phthalimides (**12f**, Phth = phthalimido), epoxides (**12j**), and complex scaffolds such as carbohydrates and steroids (**12k**−**m**). The steroid examples are particularly interesting: they illustrate the modification of the side chain by having either the vinylsulfone or the xanthate on the steroid partner. Developing new strategies for the construction of steroid side chains remains a worthwhile endeavor, especially in the context of vitamin D_3 derivatives.[20]

Finally, complexity may be introduced in a modular fashion. For instance, xanthate **4e** is made by radical addition of a simpler mesityl oxide-derived xanthate [MeC(=O)CH_2CMe_2SCSOEt, **4j**] to vinyl pivalate,[21] so each of the resulting vinylsulfones **12e** and **12i** is in fact constructed from four different components: an aldehyde, phenyl vinyl sulfide, vinyl pivalate, and xanthate **4j**.

A simple, flexible, and powerful process for the synthesis of alkenes with defined geometry is now in hand. A few illustrative examples are displayed in Scheme 4. Thus, reductive desulfonylation of **12b** gives (*Z*)-alkene **13b** in 76% yield, whereas addition−fragmentation of xanthate **4k** to glucose-derived vinylsulfone **10g** furnishes carbohydrate (*Z*)-alkene **13c** via intermediate (*E*)-vinylsulfone **12m** in good overall yield. It is interesting to note that radical addition−fragmentation on the naked vinyl alcohol derivative **18** cleanly and directly gives (*E*)-alkene **17b**.[13] Both (*Z*)- and (*E*)-alkenes may therefore be prepared through the inclusion or omission of the phenylsulfonyl group. The stereoselective obtention of trisubstituted alkenes combines the radical addition−fragmentation with organometallic coupling reactions of vinylsulfones developed by Julia and others,[22] as shown by the conversion of vinylsulfones **12a** and **12d** into (*Z*)-alkenes **20a** and **20b**, respectively, through $Ni(acac)_2$-mediated couplings.

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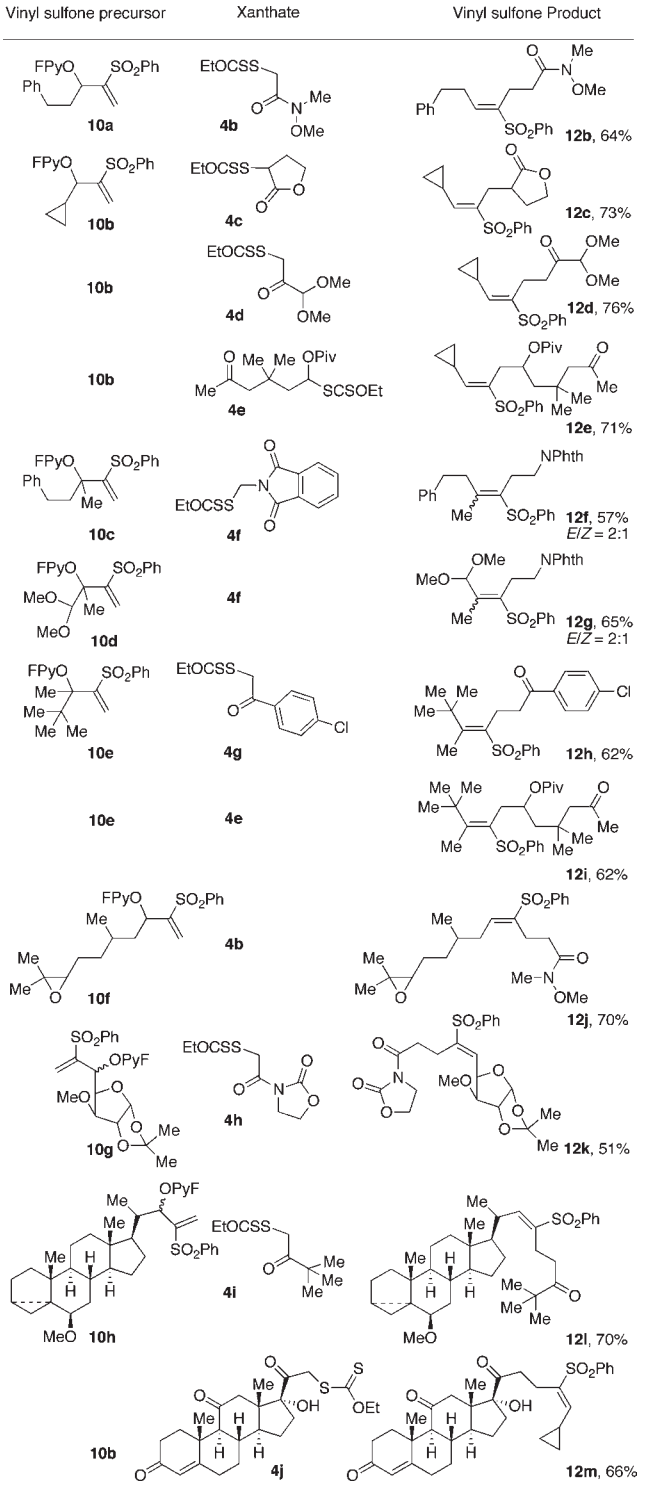
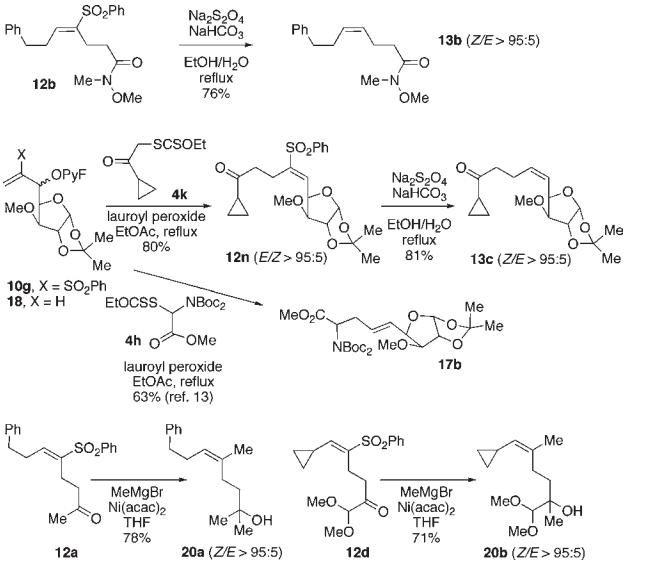
Table 1. Stereoselective Synthesis of (*E*)-Vinylsulfones



The couplings proceed with retention of stereochemistry, and the ketone groups are converted in both cases into the corresponding carbinols by direct reaction with the excess methyl Grignard reagent present. More elaborate organometallic reagents may be used if needed (cf. ref 22f).

In summary, we have described a convergent, flexible, and modular approach to both (*E*)- and, especially, (*Z*)-alkenes that ultimately hinges on the *slow homolytic rupture* of a fluoropyridinoxy group, which allows control of the stereochemistry of the key intermediate vinylsulfones. Not only are numerous functional groups tolerated, but the vinylsulfone motif itself has an exceptionally rich chemistry that may be exploited for the synthesis of myriad other products.[23]

Scheme 4. Stereoselective Synthesis of Di- and Trisubstituted (*Z*)-Alkenes



■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures as well as a compilation of spectral and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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